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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,713	08/25/2003	Jonathan Stamler	102258.121 US3	9858

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WILMERHALE/NITROMED
1875 PENNSYLVANIA AVE, NW
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EXAMINER	
GHALI, ISIS A D	
ART UNIT	**PAPER NUMBER**
1615	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS **from the mailing date of this communication.**

Office Action Summary	Application No.	Applicant(s)	
	10/646,713	STAMLER ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2006* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,8,12,13,15,19,20,22,26,27,29,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,8,12,13,15,19,20,22,26,27,29,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The receipt is acknowledged of applicants' amendment filed 11/16/2006.

Claims 2-4, 7, 9-11, 14, 16-18, 21, 23-25, 28, 30-32, 35 have been canceled.

Claims 1, 5, 6, 8, 12, 13, 15, 19, 20, 22, 26, 27, 29, 33, and 34 are pending and included in the prosecution.

The following rejections have been overcome by virtue of applicants' amendment and remarks:

(A) The rejection of claims 5-7, 12-14, 19-21, 26-28, and 33-35 under 35 U.S.C. 112, first paragraph as the specification failed to provide enablement for specific compounds as anti-thrombogenic agents.

(B) The rejection of claims 6-7, 13-14, 20-21, 27-28, and 34-35 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following rejections have been discussed in details in the previous office action, and are maintained for reasons of record:

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 5, 6, 8, 12, 13, 15, 19, 20, 22, 26, 27, 29, 33, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To satisfy the Written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that applicant were in possession of the claimed invention. Applicants' claims are drawn to ACE inhibitor which has at least one –O-NO_2 group. The specification gives no guidance to one skilled in the art for description of ACE inhibitor which has at least one –O-NO_2 group and no structure given to ACE inhibitor has at least one –O-NO_2 group. With careful recourse to the specification, the examiner notices that at pages 17-21 applicants disclosed ACE inhibitors, however, none of the disclosed ACE inhibitors has –O-NO_2 group. The disclosed ACE inhibitors on pages 17-21 all have NO (nitroso- group). On the other hand, on page 23 applicants disclose NO (nitric oxide) adducts that have –O-NO_2 group and they do not include any ACE inhibitors. Clarification is requested. Nowhere applicants have described ACE inhibitor has at least one –O-NO_2.

Response to Arguments

3. Applicant's arguments filed 11/16/2006 have been fully considered but they are not persuasive. Applicants traverse this rejection by arguing that the specification on page 23 disclosed NO adducts having –O-NO_2 group, wherein NO adducts include compounds such as polypeptides, and ACE inhibitors are polypeptides.

In response to this argument, the examiner disagree that ACE inhibitors are polypeptides. Provided are two articles showing the structure of ACE inhibitors showing no –O-NO_2 group in their structure. The articles are "Physicians' Desk References" and the article "Synthesis of angiotensin-converting enzyme (ACE) inhibitors: an important class of antihypertensive drugs". Accordingly, ACE inhibitors are not polypeptide, and do not have –O-NO_2 group. Additionally, even ACE inhibitors are polypeptides, they not disclosed by applicants as containing –O-NO_2 group.

4. Claims 1, 5, 6, 8, 12, 13, 15, 19, 20, 22, 26, 27, 29, 33, and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method for inhibiting adverse effects associated with use of medical device in patient wherein the device include nitric oxide adduct for local delivery at the site of contact of a device or instrument containing NO with the blood, does not reasonably provide enablement for inhibiting platelets deposition in a patient in general, not at the site of contact of device and blood, by any other local routes of administration of NO. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the breadth of the claims; the state of the prior art; the relative skill of those in the art; the amount of direction or guidance presented; the predictability or unpredictability of the art; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The nature of the invention: The nature of the invention is method for inhibiting platelets aggregation in a patient by administering NO adduct locally.

The breadth of the claims: The claims are broad. The claims encompass all method of inhibiting platelets aggregation in a patient that encompasses any site where platelets can aggregates, and all inhibited by local administration of NO including, transdermal, implant, or rectal, etc. The claims also encompass inhibiting of platelets aggregation in any organ and caused by any causes. The entire specification disclosed local delivery of NO from devices or instruments contacting the blood, page 5, 14 and 15. Nowhere in the specification applicants disclosed other methods for administering NO. The specification also does not disclose inhibiting platelet aggregation any where in the patient, but only at site of contact of medical device with blood.

The state of the prior art: The state of the art recognized the inhibitory effects of NO on platelets aggregation by administering NO adduct such as ACE inhibitors intravenously, transdermally, orally, or as a suppository, US 5,002,964 and US 5,025,001. However, the art does not recognized NO adduct containing nitrate group administered as a coating, incorporation in the material or as derivatizing to the surface of the medical devices and instrument.

The relative skill of those in the art: The relative skill of those in the art is high.

The amount of direction or guidance presented: The specification provides no guidance, in the way written description, on inhibiting platelets deposition in a patient other than platelets deposition associated with use of medical devices or instruments that contact the blood. The specification provides no guidance, in the way written description, on the administration of NO by local routes other than inclusion in devices and instruments that contact the blood as coating, inclusion in the material of the device, or by derivatizing the surface of the device, page 5, lines 23-30. It is not obvious from the disclosure of inhibiting platelets aggregation associated with the use of medical devices that contact the blood that platelets aggregation in general, such as brain clots, will be inhibited in a patient by using such devices and instruments. It is not obvious from the disclosure of delivery of NO by inclusion in devices and instruments that contact the blood if the other methods of local administration will provide the same platelets aggregation inhibitory effect. It must appear in an applicant's specification either by the enumeration of a sufficient number of administration methods or by other appropriate language, that other methods of administration encompassed by the claims

are capable of accomplishing the desired result. A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the administration methods fall within the scope of a claim will possess the alleged activity.

The predictability or unpredictability of the art: The lack of guidance from the specification and from the prior art with regard to inhibiting platelets aggregation in a patient using NO adduct by local administration in or on a medical device makes practicing the claimed invention unpredictable in the terms of the method of inhibiting platelets deposition and method of administration of NO adduct.

The presence or absence of working examples: The specification discloses method of inhibiting platelets deposition associated with the use of medical devices only, and not all causes of platelets aggregation. The specification disclosed NO adduct included in devices or instruments that contact patient's blood. Therefore, the specification has enabled inhibiting platelets deposition in a patient associates with use of medical devices or instruments that contact the blood. Additionally, the specification has enabled local administration of NO by inclusion in devices and instruments contacting blood as shown by the examples as a coating, inclusion in the material of the device or by derivatizing the surface of the device.

The quantity of experimentation necessary: Therefor, the practitioner would turn to trial and error experimentation to practice the instant method for inhibiting all platelets aggregation in a patient from different causes by all known methods of local

administration of drugs without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

Response to Arguments

5. Applicant's arguments filed 11/16/2006 have been fully considered but they are not persuasive. Applicants traverse this scope of enablement rejection by arguing that the amendment of the claims to recite "associated with the use of medical device" rendered the rejection moot because the specification is enabled for "adverse effects associated with the use of medical device in patients wherein the device include nitric oxide adduct".

In response to this argument, applicants' attention is directed to the scope of the claims as amended, which is method of inhibiting platelets deposition that happens with use of medical device, the method comprises local administration of NO adduct. The claims as amended do not recite "device include nitric oxide adduct" as asserted by applicants. The scope of the claims encompass any medical device such as needle, casts, etc. and encompass any local administration of NO adduct including all local routes of drug administration such as cream, gel, lotion, or transdermal patches, etc. The specification disclosed specific medical devices on page 5, lines 20-22, including: "catheter, prosthetic heart valve, synthetic vessel graft, stent, arteriovenous shunt, artificial heart, intubation tubes". The specification disclosed specific local routes for administration NO adducts on page 5, lines 23-30 by disclosing: "local routes by inclusion in devices and instruments that contact the blood as coating, inclusion in the

material of the device, or by derivatizing the surface of the device". It is not obvious from the disclosure of delivery of NO by inclusion in specific devices and instruments that contact the blood if the other methods of local administration will provide the same platelets aggregation inhibitory effect.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 8, 15, 22 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,025,001 ('001).

US '001 disclosed method for treating myocardial infarction, angina pectoris, and vascular thrombosis by administering ACE inhibitors having the same structures disclosed by applicants locally, i.e. transdermally, to inhibit platelet aggregation (abstract; col.8, line 31-col.15, line 53; col.17, lines 1-2; col.25, lines 58-60, 69).

8. Claims 1, 8, 15, 22 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,002,964 ('964).

US '964 disclosed method for inhibiting platelet aggregation and treating myocardial infarction, angina pectoris, and vascular thrombosis by administering ACE

inhibitors having the same structures disclosed by applicants locally, i.e. transdermally or as a suppository (abstract; col.4, line 31-col.9, line 34).

Response to Arguments

9. Applicant's arguments filed 11/16/2006 have been fully considered but they are not persuasive. Applicants traverse the anticipatory rejections by arguing that the ACE inhibitors disclosed by US '001 and US '964 do not contain $-O-NO_2$ group but contain –SNO group, and the two groups are structurally different.

In response to this argument, applicants' attention is drawn to their disclosure on pages 17-23 wherein the structures of ACE inhibitors is disclosed, and they are identical to the structures disclosed by US '001 and US '964. If applicants admit that the structures of ACE inhibitors disclosed by the references do not have $-O-NO_2$ group, then they admit that the ACE inhibitors they disclosing also do not have $-O-NO_2$ group.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 5, 6, 12, 13, 19, 20, 26, 27, 33, and 34 rejected under 35 U.S.C. 103(a) as being unpatentable over any of US '001 or US '964 in view of Fuster et al.

The teachings of US '001 and US '964 are discussed above.

However, the references do not teach the administration of other active agent along with the NO adduct.

Fuster et al teach anticoagulant including aspirin, prostaglandin and heparin have anti-platelet aggregation effect (the entire document).

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to deliver ACE inhibitor locally to inhibit platelets aggregation as disclosed by any of US '001 and US '964, and add anticoagulant to the ACE inhibitors as disclosed by Fuster, motivated by the teaching of Fuster that anticoagulant have anti-platelets aggregation effect, with reasonable expectation of having synergistic inhibiting platelets aggregation effect using both ACE inhibitors and anticoagulant locally.

Response to Arguments

13. Applicant's arguments filed 11/16/2006 have been fully considered but they are not persuasive. Applicants traverse this rejection by arguing that Fuster does not cure the deficiencies of US '001 and US '964, and provides no motivation to modify the references to arrive to the claimed invention.

In response to this argument, it is argued that US '001 and US '964 disclosed ACE inhibitors having the same structures as disclosed by applicants. Fuster is relied upon for the solely teaching of administration of anticoagulant including aspirin, prostaglandin and heparin that have anti-platelet aggregation effect in patients with atherosclerotic disease or following coronary angioplasty. Note the claims' language does not require any specific route or any specific time for administering anti-thrombogenic compounds. One having ordinary skill in the art at the time of the invention would have been motivated to administer one of the compounds disclosed by Fuster to the patient receiving ACE inhibitors locally to prevent platelets aggregation as disclosed by US '001 or US '964, motivated by the teaching of Fuster that anticoagulant have anti-platelets aggregation effect, with reasonable expectation of having synergistic inhibiting platelets aggregation effect using both ACE inhibitors and anticoagulant.

It is well established that the claims are given the broadest interpretation during examination. A conclusion of obviousness under 35 U.S.C. 103 (a) does not require absolute predictability, only a reasonable expectation of success; and references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosure. *In re Bozek*, 163 USPQ 545 (CCPA 1969).

In the light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the claims would have been *prima facie* obvious within the meaning of 35 U.S.C. 103 (a).

Conclusion

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone

number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Isis A Ghali
Primary Examiner
Art Unit 1615

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